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EDITORIAL COMMENT

Percutaneous Left Main Invention

An Evolving Perspective*

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"Third PCI patient ever treated. Forty-three year old man with severe angina pectoris since September, 1977. First angiogram (November 11) revealed severe stenosis of the main L.C.A. . ." (see Fig. 1). (The patient expired suddenly about 4 months after this procedure.)

—Gruntzig (1)

"From a large prospective randomized study, data relating to a subgroup of 113 patients with angina pectoris and a significant lesion of the left main coronary artery were analyzed. The proportion surviving 24 months was clearly larger in the surgically treated group ($p < 0.02$)."

—Takaro (2)

Consequent principally to the demonstration of survival benefit with bypass surgery compared with optimal medical therapy in the VA Cooperative Trial in 1976 (2), but also due to poor initial results and the unpredictability of early balloon angioplasty in this setting (1,3), bypass surgery became the standard treatment for unprotected left main coronary disease (ULMT) and percutaneous coronary intervention (PCI) was strongly discouraged.

See pages 584, 595, 602, 612, 624, and 632

Balloon angioplasty was occasionally performed, however, especially for patients with very high expected surgical risk. As PCI results became more predictable in the late 1980s, first with directional coronary atherectomy and later with stenting, intrepid investigators, particularly from Asian societies shunning surgically invasive procedures, (e.g., S. J. Park, Hideo Tamai, Masakiyo Nobuyoski) and elsewhere (e.g., Carlos Macaya, Antonio Colombo) began to experiment with a more routine use of PCI for ULMT disease (4,5).

We had the opportunity to initiate a collaborative effort to collect consecutive cases from experienced laboratories from 1993 to 1998. This, the largest study of its kind at the time, demonstrated in 279 patients considerable heterogeneity of results, but excellent outcomes in the subgroup of patients <65 years old with left ventricular ejection fraction >30% and no cardiogenic shock (no periprocedural and 3.4% 1-year mortality). One-year post-discharge mortality was worrisomely high (10%) and related more to left ventricular function than extent of coronary artery disease, raising questions about the impact of restenosis of this critical site in patients with impaired left ventricular function (6,7).

Several key advances have occurred since the 1990s, leading to yet safer results: better antiplatelet therapy, the use of intravascular ultrasound, and drug-eluting stents (DES), in particular. Optimal medical therapy including statin use is also important.

As the results from more current registries proved encouraging, the impetuous was provided for randomized trials to gain more definitive answers about optimal treatment. Now that we have 2-year follow-up results from the randomized SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (8), it is worth reflecting upon where the present knowledge base stands.

Before doing so however, we should review the role and limitations of both registries and randomized clinical trials (RCTs). Registry results reflect outcomes after the physicians have chosen what they believe to be the best treatment for each patient. Patients treated with PCI or bypass surgery are inherently different. Registry results are typically incompletely monitored for quality. One need only to recall the conclusions of previous registries—that DES kill patients compared to bare-metal stents (BMS) (SCAAR [Swedish Coronary Angiography and Angioplasty Registry]) (9), that birth control pills are cardioprotective against atherothrombosis in post-menopausal women, not to mention that mega meta-analyses of registries suggest DES are associated with a 20% reduction in mortality compared with BMS (a finding that has absolutely no replication when meta-analysis is confined to RCT)—to understand the limitations of registry data. Even propensity analysis, in its various iterations, has major limitations: 1) If the model predicting treatment allocation is quite good, then there are very few patients with overlapping risks to be studied. 2) If the predictive model is poor, then there really is no risk adjustment. Poor understanding of these concepts is especially relevant in this era of "comparative effectiveness research," with the risk that careless interpretation of study data will lead to bad policy emanating from Washington, D.C. On the other hand, RCT results often suffer from suspect external validity. For example, patients recruited for such trials are often not typical of those in clinical practice,

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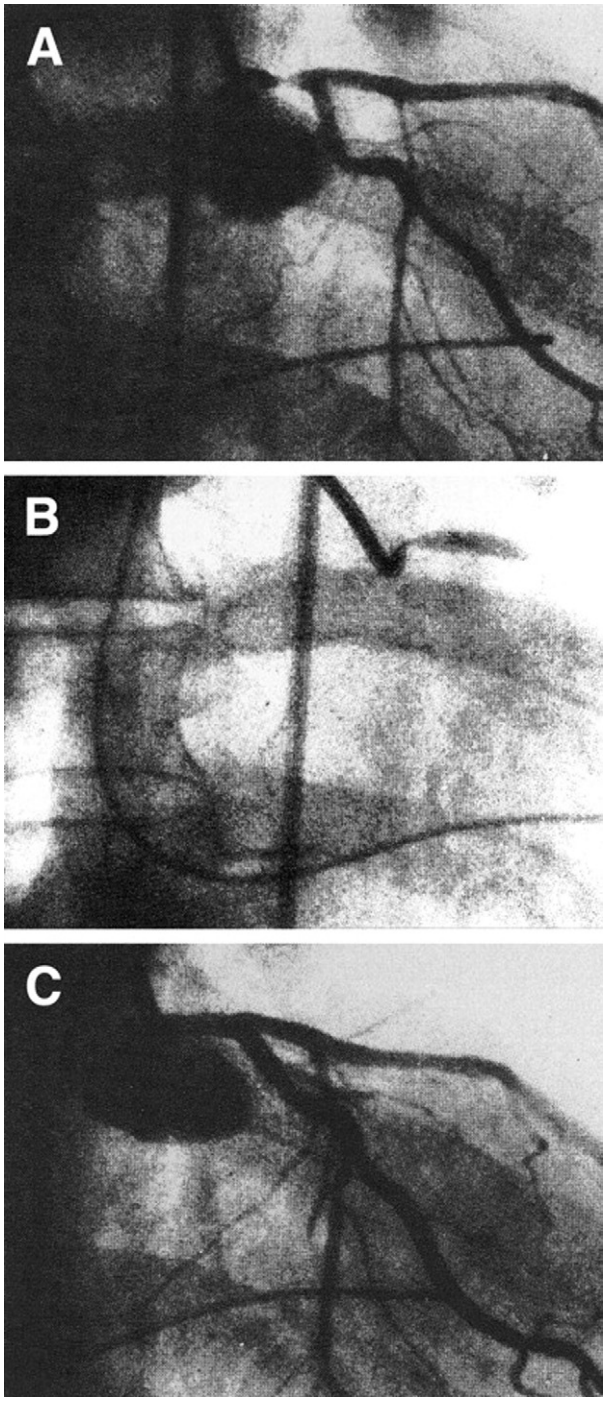

Figure 1. Balloon Angioplasty Patient's Coronary Lesion and its Treatment

Still frame images of Dr. Gruntzig's third balloon angioplasty patient's coronary lesion and its treatment. Reprinted with permission from Gruntzig et al. (1).

often being younger and with fewer clinical comorbidities. Importantly, as differential direction of treatment effect among subgroups is rare, a logical analytic sequence is to perform registry analyses of patients excluded from RCTs after the treatment benefit of the given intervention has been demonstrated in RCTs, so as to give insight as to whether or not the RCT results are generalizable (acknowledging the limitations of registry data). Randomized trials also have to have sufficient sample size to have power be "certain" of results and use end points chosen for their clinical meaningfulness and not for sample size convenience. Lastly, but most importantly perhaps, is the recognition that patients are different and that "one size doesn't always fit all."

In this issue of *JACC: Cardiovascular Interventions,* 6 articles attempt to extend knowledge in this particular clinical realm.

Three of these reports focus on defining factors predictive of outcomes with percutaneous and/or surgical intervention. Kim et al. (10) report results of application of the SYNTAX score in 819 PCI and 761 bypass patients from a large multicenter Asian registry. Patients were followed for 3 years. The SYNTAX score was modestly predictive of 3-year outcomes in patients treated with DES, less predictive with outcomes after placement of BMS, and very poorly predictive of long-term outcomes after bypass surgery. The SYNTAX score tertile was not helpful in discrimination of risk between PCI and bypass surgery (in contradistinction to the prediction of 1-year outcomes in the SYNTAX trial itself). Other studies have shown variable outcomes. Kim et al. (10) suggest that parameters describing clinical risk profile might be useful in conjunction with scores such as the SYNTAX score, which focus on patient anatomy. In particular, their results draw focus to the impact of chronic renal insufficiency, prior congestive heart failure or cerebrovascular disease, diabetes, and chronic lung disease. Chen et al. (11) compare the predictive value of the SYNTAX score and a broad-based, 51-element NERS (Novel Risk Stratification) score derived from analysis of a prior ULMT PCI registry, on major adverse cardiac events. The latter score significantly outperformed the SYNTAX score for several outcomes, but as the original model was clearly overfitted (126 variables tested, 260 patients), it is likely this score could be appreciably refined and improved. Tamburino et al. (12) report the for the first time a novel approach, correlating the location of left main trunk bifurcation plaque distribution and outcomes in 329 consecutive patients undergoing left main stenting from 2 Italian centers. Patients with plaque occupying "the whole bifurcation" were found to be at higher risk of subsequent need for target lesion revascularization regardless of stenting technique.

Three other reports take a more general look at long-term outcomes after treatment of ULMT patients. Onuma et al. (13) report the Thoraxcenter experience from 2000 to 2005 with DES in 148 patients, compared with a historical control cohort of 79 patients treated with BMS. The investigators find both the EuroSCORE (European System

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 6, 2010
JUNE 2010:642–7

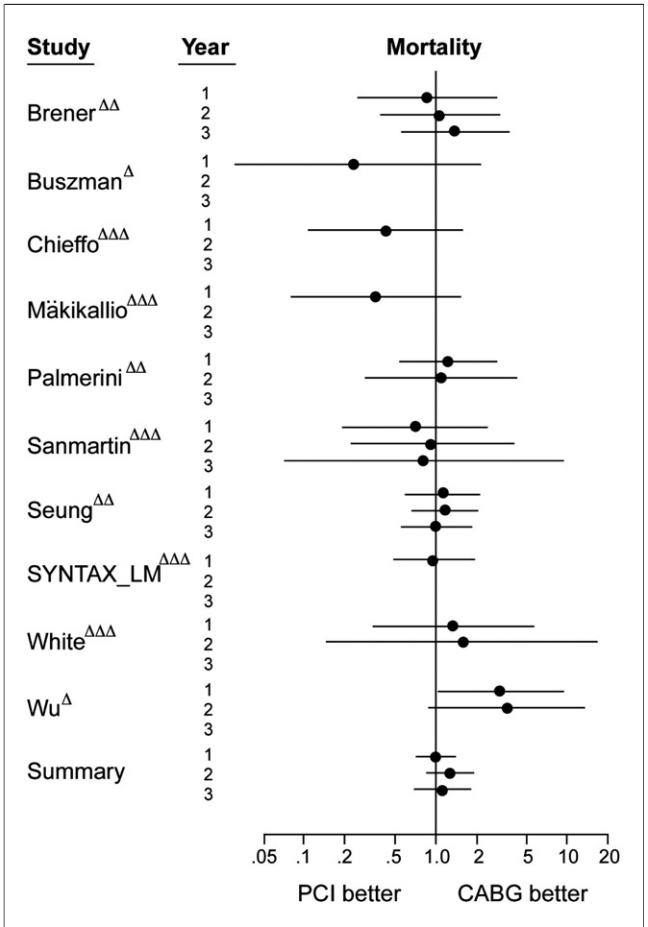

Figure 2. Odds Ratio of MACE Following Treatment for ULMCA in Registries and RCT

Odds ratio of major adverse cardiovascular events (MACE; death, myocardial infarction, cardiovascular accident) following treatment for unprotected left main coronary artery disease (ULMCA) in percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) patients. Modified from Naik et al. (28). Δ = predominantly bare-metal stents; ΔΔ = predominantly drug-eluting stents; ΔΔΔ = all drug-eluting stents.

for Cardiac Operative Risk Evaluation) and SYNTAX score to be correlated with 4-year outcomes. The overall case mix was complex with nearly a quarter of patients presenting with ST-segment elevation myocardial infarction, 8.8% with shock. Anatomy was also complex, with a SYNTAX score of almost 40. As such, perhaps the 1-year all-cause mortality of 19.6% was not particularly surprising. The investigators draw attention, however, to adverse outcomes apparent in follow-up years 3 and 4—the 10% risk of death, in particular.

Pandya et al. (14) report a meta-analysis of studies comparing DES and BMS in this setting, following patients for up to 3 years after PCI. Both crude and adjusted data are provided. The investigators caution about the concern of confounding and selection bias, and suggest that direct comparison of the overall BMS and DES rates not be performed. That said, the investigators report similar 6- to 12-month mortalities and a very considerable reduction in the need for target vessel/lesion revascularization with DES. By 3 years, results favored DES for mortality and myocardial infarction and target vessel/lesion revascularization. Lastly, Chieffo et al. (15) report on 5-year outcomes from a single Italian center, comparing findings after PCI and bypass surgery. Two-hundred forty-nine patients were included at 5 years, and PCI appeared to be associated with a lower rate of the composite adverse outcome of death, myocardial infarction, or stroke, whereas bypass surgery was correlated with lower target vessel revascularization. There was no significant difference relating treatment to the occurrence of cardiac death. Interestingly, there was nearly 6% incidence of stent thrombosis.

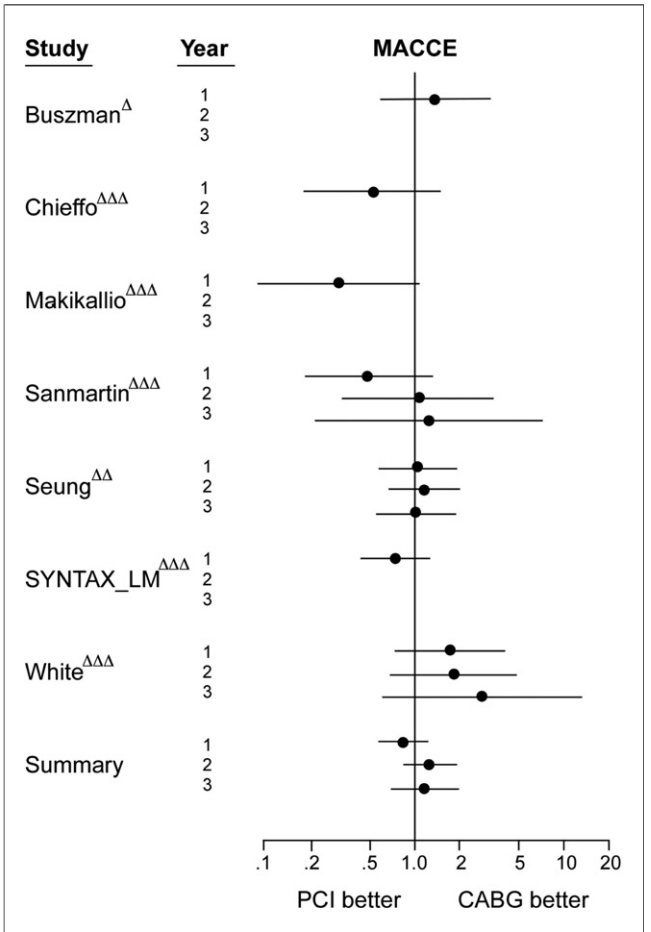

Figure 3. Odds Ratio of Mortality Following Treatment for ULMCA in Registries and RCT

Odds ratio of mortality following treatment for unprotected left main coronary artery disease in percutaneous coronary intervention versus coronary artery bypass graft patients. Modified from Naik et al. (28). Δ = predominantly bare-metal stents; ΔΔ = predominantly drug-eluting stents; ΔΔΔ = all drug-eluting stents. MACCE = major adverse cardiac and cerebrovascular events; other abbreviations as in Figure 2.

Table 1. Selected Studies of Stenting Versus Bypass Surgery for ULMCA

First Author (Ref. #)	Single or Multicenter	Patients	DES (%)	Risk Adjustment	Follow-Up Duration	(CV) Death		MI		Stroke		Death, MI, or Stroke		TVR/TLR		Limitations
						Stent	CABG	Stent	CABG	Stent	CABG	Stent	CABG	Stent	CABG	
Brener et al. (19)	S	287	57	Propensity	3 yrs	20.0	15.0									Nonrandomized, underpowered, end point details NA
Chieffo et al. (20)	S	249	100	Propensity	1 yr	2.8	6.4	0.9	1.4	0.9	0.7			19.6	3.60	Nonrandomized, underpowered
Chieffo et al. (15)	S	249	100	Propensity	5 yrs	7.5	11.7	0.9	7.7	0.9	4.2			18.7	8.4	Nonrandomized, underpowered
Makikallio et al. (21)	M	287	100	None	2 yrs	4.0	11.0	2.0	2.0	0	5.0			4.0	2.0	No adjustment for between-group differences, very limited number of DES patients, underpowered, short duration of follow-up
Palmerini et al. (22)	M	311	60	Propensity	2 yrs	7.4	9.7	5.3	4.5					22.0	2.6	Nonrandomized, underpowered, adjusted, and end point details NA
Sanmartin et al. (23)	S	341	100	Propensity	3 yrs	9.0	11.0					9.0	17.0	16.0	3.0	Nonrandomized, underpowered
Serruys et al. (24)	M	705	100	RCT	2 yrs	4.2*	4.4*	4.3*	4.1*	0.3*	2.7*	10.2	11.8	17.3	10.4	Subgroup of a technically negative trial, somewhat underpowered, limited duration of follow-up
Seung et al. (18)	M	792	100	Propensity	3 yrs	9.0a	6.9a					12.5a	8.0a	9.3a	1.6a	Nonrandomized
White et al. (25)	S	343	100	Propensity	30 months	18.9	12.7									Nonrandomized, underpowered, end point details NA
Kim et al. (10)	M	1,580	79	SYNTAX score	3 yrs	6.2	9.2					7.1	10.4	10.3	2.7	Nonrandomized

*Drug-eluting stents >50% of percutaneous coronary intervention; DES-specific data only (when provided): a = adjusted (otherwise unadjusted) + 1-year outcomes.

CABG = coronary artery bypass graft; CV = cardiovascular; DES = drug-eluting stent; M = multicenter; MI = myocardial infarction; NA = not available; RCT = randomized clinical trial; S = single center; TLR = target lesion revascularization; TVR = target vessel revascularization; ULMCA = unprotected left main coronary artery disease.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 3, NO. 6, 2010
JUNE 2010:642–7

Treatment of this relatively small group of anatomically unique patients, whose importance has perhaps been magnified because they represent the "last bastion" of patients requiring open heart surgery, draws an emotionally charged focus from competing surgeons and interventionalists. (The true "last bastion" is more likely patients with diffuse but bypassable disease.) Therefore, a knowledge base for treatment needs to be synthesized (Figs. 2 and 3, Table 1) (16–25), but the following information is necessary to complete it. 1) There is still work to be done about discerning among this group who would best be treated with each of the revascularization strategies. Data from Kim et al. (10), Chen et al. (11), and Park et al. (5) suggest caution in using the SYNTAX score alone to make this determination. Perhaps this is intuitive, but better scoring methodology needs to be flushed out from large groups of patients and carefully studied. 2) The cardiology community needs longer-term follow-up from large studies in which patients were randomized to either of these 2 revascularization strategies. The 12- to 24-month data from the SYNTAX trial, wherein the event curves of the DES and surgically treated patients are largely parallel, are reassuring, but the appropriate time horizon for patients such as this, particularly when an invasive surgical procedure is being contemplated, should be at least 5 years. Long-term data from the Thoraxcenter is perhaps somewhat disturbing in this regard. However, readers should be mindful of the high-risk mix of patients studied and also their very small number. Conversely, most large reports of DES-treated patients of different levels of complexity show relatively flat event curves 2 to 5 years after PCI (18,26,27).

At this point, because ULMT patients need treatment today, perhaps we can agree that most patients with very few simple lesions in addition to their left main narrowing (typically falling into the lowest SYNTAX score tertile) (e.g., see Fig. 3A of Kim et al. [10]), and who can tolerate dual antiplatelet therapy, be considered quite reasonable candidates for referral for PCI. Conversely, patients with advanced and multiple lesions (characteristically falling into the highest risk tertile of the SYNTAX score) are probably best referred for open heart surgery. There remains a relatively large number of patients with intermediate anatomic complexity, as well as many other subsets of patients for which we have incomplete data (e.g., chronic renal insufficiency) for whom there remains considerable uncertainty. Although we will have to be patient, hopefully we will receive more information on these patients from the upcoming EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial.

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